Docket No. 2551-1-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS: Hassan Ahmad & Ismail Elchagea

EXAMINER: McCormick Ewoldt, Susan Beth

SERIAL NO.: 10/662,777

ART UNIT: 1654

FILED: September 15, 2003

TITLE: BOTANICAL DRUG COMPOSITIONS FOR TREATMENT OF LIVER AND IMMUNOLOGICAL DISORDERS

CERTIFICATE OF MAILING UNDER 37 CFR 1.8

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on April 3, 2006.

Loretta Kavanagh
(Name of person Depositing Mail)

Loretta Kavanagh
(Signature and Date)

DECLARATION PURSUANT TO 37 C.F.R. § 1.132 OF HASSAN AHMAD

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, HASSAN AHMAD, do hereby declare as follows:

1. I am Chairman and Chief Executive Officer of Ambotan Pharmaceuticals.

2. My principal area of research is in Natural Products and Pharmaceutical Research and Drug Development, with particular expertise in infectious diseases.

3. I am listed as an inventor on the present patent application, entitled "BOTANICAL DRUG COMPOSITIONS FOR TREATMENT OF LIVER AND

IMMUNOLOGICAL DISORDERS", U.S. Serial Number 10/662,777, filed September 15, 2003.

4. I have reviewed the disclosure of the present application, with particular emphasis on the pharmaceutical compositions under development for treating patients with advanced stage liver disease and immunological disorders. Our laboratory has identified the plants and extracts of this application as being efficacious for treating patients having advanced stage hepatitis, which is characterized as being of stage 4-6, with evidence of fibrosis and cirrhosis of the liver. A summary of certain of our findings is attached here as Exhibits A and B.

5. To my knowledge there are no effective therapies to reverse or stabilize the liver damage observed in late stage 4-6 of hepatitis. Furthermore, to my knowledge, no others have used an extract from any one plant of our invention, namely *Actaea rubra, Anemone hepatica, Anemone nemorosa, Nigella-sativa, Ranunculus arvensis* or a composition consisting of an extract of any one of these plants to stabilize or reverse the histopathological effects of hepatitis, including liver fibrosis and cirrhosis associated with stages 4-6 hepatitis. Nor has anyone used the extract from any one of these plants or a composition consisting of an extract of any one of these plants to lower the hepatitis viral load in the serum of patients as we have shown.

6. I have reviewed the references by Shawkat and by Shalaby. Both Shawkat and Shalaby use an herbal composition containing a mixture of plants for treating viral diseases, including hepatitis. Shawkat and Shalaby do not treat stage 4-6 hepatitis patients with any extract from any one of the plants of our invention, in particular, *Nigella sativa*. More particularly, neither Shawkat nor Shalaby use an extract from any one particular plant of our invention for treating hepatitis patients in stages 4-6 having signs of fibrosis or cirrhosis, or for reversing the histopathological changes in the liver of these patients, or for decreasing the viral load in the serum of these patients.

7. Neither Shawkat nor Shalaby use an extract from only one plant as described in our present invention, particularly *Nigella sativa*, for elevating either the number or activity of immune cells or platelets in stage 4-6 hepatitis patients having fibrosis or cirrhosis. In addition, neither Shawkat nor Shalaby demonstrate the lowering of hepatitis viral load using a composition consisting of one plant extract, in particular, *Nigella sativa* at a concentration of not less than 20% weight per volume.

8. We have demonstrated that the most significant efficacy of an extract of one of the plants, in particular, *Nigella sativa,* the major component of Ambovex, when used alone, must be administered in a concentration of not less than 20% weight per volume. For example, an extract of *Nigella sativa* was tested at a low (<15%) and a high (>20%) concentration in a recent clinical trial. In clinical studies, patients having greater than 2 million copies of Hepatitis C genotype 4 were randomized to Placebo (P) or Ambovex (Amb) treatment groups. As noted above, the active component in Ambovex is an extract from *Nigella sativa*. A number of studies were conducted, lasting from 6 months to 36 months. Ambovex patients, but not placebo patients, showed decreased viral load, as measured by a decrease in hepatitis virus RNA.

In clinical trials, three sets of stage 4-6 hepatitis patients, having signs of fibrosis or cirrhosis and exhibiting a significant viral load in the serum, were treated with Ambovex (*Nigella sativa)* at two different concentrations or with placebo. The low concentration consisted of less than a 15% weight per volume extract, while the high concentration consisted of a concentration of greater than 20%. The patients were administered three, one milliliter doses per week in the first year, and one, one milliliter dose per week in the second and third year, each dose being administered intramuscularly. Blood was collected in follow-up visits at the following time points for the low dose group: 6 months and 12 months. Blood was collected from the high dose group at the following time points: 6 months, 12 months, 24 months and 36 months. The serum was tested for hepatitis C viral RNA using polymerase chain reaction (PCR).

As shown in the following Tables 1 and 2 (in Exhibits A and B), there was evidence of a low percentage of patients showing modest efficacy using the low dose extract. For

example, at 6 months, 10% of the patients showed a decrease in viral load by one log, and 23% of the patients showed a decrease in viral load of 70% or greater. None of the low dose patients demonstrated viral RNA levels below the level of detection (BLOD). By 12 months of treatment, only 7.4% of the low dose patients being treated showed a decrease in viral load of one log and 17% of the low dose patients being treated showed a decrease in viral load of about 70%. Once again, none of the patients being treated with low dose demonstrated viral RNA levels below the level of detection.

On the other hand, the number of patients responding to the high dose of Ambovex (*Nigella sativa*), eg. greater than 20%, was significantly higher than the number in the low dose group. In fact, by 6 months after initiation of dosing, 20% of patients showed a decrease in viral load by one log, and 34% of the patients in the high dose group showed a decrease in viral load by 70%. Furthermore, 6% of the patients were below the level of detection (BLOD). This trend continued throughout the 12 month to 36 month trial period. By 12 months, 29% of the patients showed a decrease in viral load by one log, and 45% of the patients in the high dose group showed a decrease in viral load by 70%. Furthermore, 10% of the patients were below the level of detection (BLOD). By 24 months, 34% of the patients showed a decrease in viral load by one log, and 63% of the patients in the high dose group showed a decrease in viral load by 70%. Furthermore, 12% of the patients were below the level of detection (BLOD). By 36 months, 43% of the patients showed a decrease in viral load by one log, and 55% of the patients in the high dose group showed a decrease in viral load by 70%. Furthermore, 18% of the patients were below the level of detection (BLOD).

Given the serious nature of the disease at such a late stage, such positive findings were unexpected. Furthermore, we were only able to observe the unexpected results in improvement of liver function tests, improved histopatholgy and improvement in immune cell number and function in this patient population by increasing the dosages to at least 20% w/v.

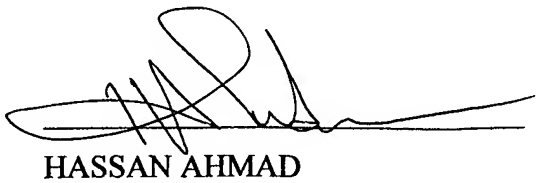
Lower doses were not effective in reversing the histopathology or immune function or immune cell numbers in these patients. Shawkat and Shalaby did not demonstrate such unexpected findings using one plant extract alone at the doses we utilized in our studies,

in particular, *Nigella sativa*. Both Shawkat and Shalaby demonstrated their effects using a mixture of plants. Thus, the efficacy of their plant mixture is in all likelihood a result of the combination of the plants used. Neither Shawkat nor Shalaby prepared and showed efficacy with an extract of *Nigella sativa* for use as a single agent at the concentrations we used.

9. Ambovex patients, but not placebo patients, showed improvements in liver function tests, including ALT and AST. In addition, there was a dramatic impact of Ambovex on fibrotic progression in the liver, in particular, on staging, hepatic activity index (HAI), and the presence of reticulin and collagenosis in this patient population. Ambovex also had a dramatic impact on the number of immune cells and their activity, including natural killer cells (NK), macrophages, and T cells, as well as an increase in the number of platelets. It is evident that the findings of our studies are very dramatic given the advanced stage of the disease being treated. Neither Shawkat nor Shalaby demonstrate an effect of only one plant extract, in particular, *Nigella sativa* (Ambovex) on any of these parameters in patients having advanced stage hepatitis with liver fibrosis or cirrhosis.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Title 18 of the U.S. Code, Section 1001, and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

Dated: 3/13/06



HASSAN AHMAD

EXHIBIT A

TABLE I. PCR (RNA) through twelve months of Low Dose (<15%) Ambovex Injections

CATAGORIES	Viral Load "Log_{10}"			
	Cases		Placebo	
	No.	%	No.	%
Follow Up After 6 Months				
Decreases by One Log_{10}	3	10%	0.0	0.0%
Decreases by 70% and/or more	7	23%	0.0	0.0%
BLOD*	0	0.0%	0.0	0.0%
Total Number of Patients	30		11	
Follow Up After 12 Months				
Decreases by One Log_{10}	2	7.4%	0.0	0.0%
Decreases by 70% and/or more	5	17%	0.0	0.0%
BLOD*	0	0.0%	0.0	0.0%
Total Number of Patients	27		10	

*BLOD: Below the Limit of Detection

EXHIBIT B

TABLE II. PCR (RNA) through 36 months of high dose (>20%) Ambovex Injections

CATAGORIES	Viral Load "Log_{10}"			
	Cases		Placebo	
	No.	%	No.	%
Follow Up After 6 Months				
Decreases by One Log_{10}	10	20%	0.0	0.0%
Decreases by 70% and/or more	17	34%	0.0	0.0%
BLOD*	3	6%	0.0	0.0%
Total Number of Patients	50		11	
Follow Up After 12 Months				
Decreases by One Log_{10}	14	29%	0.0	0.0%
Decreases by 70% and/or more	22	45%	0.0	0.0%
BLOD*	5	10%	0.0	0.0%
Total Number of Patients	49		10	
Follow Up After 24 Months				
Decreases by One Log_{10}	14	34%	0.0	0.0%
Decreases by 70% and/or more	26	63%	0.0	0.0%
BLOD*	5	12%	0.0	0.0%
Total Number of Patients	41		0	
Follow Up After 36 Months				
Decreases by One Log_{10}	17	43%	0.0	0.0%
Decreases by 70% and/or more	22	55%	0.0	0.0%
BLOD*	7	18%	0.0	0.0%
Total Number of Patients	49		10	

*BLOD: Below the Limit of Detection